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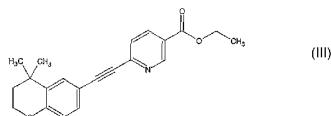
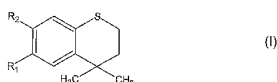
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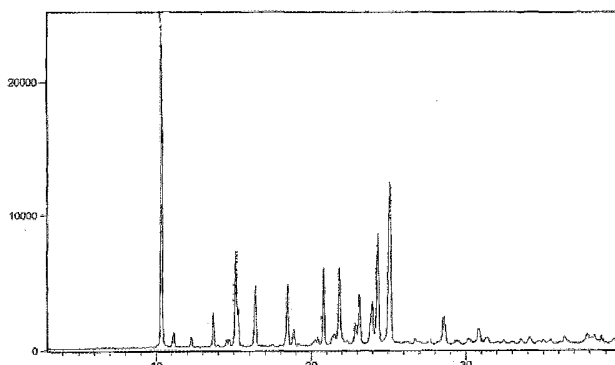
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[Continued on next page]

(54) Title: PROCESSES FOR THE PREPARATION OF SUBSTITUTED THIOCHROMAN DERIVATIVES



XRPD OF FORM A OF TAZAROTENE



(57) Abstract: The invention relates to processes for the preparation of substituted thiochroman derivatives of Formula (I), wherein R_2 is hydrogen or lower alkyl; R_1 is hydrogen, halogen, a leaving group or a group of Formula (II), wherein A is phenyl or heteroaryl selected from the group consisting of pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or and acetal derivative thereof, or -COR₃ or ketal derivative thereof, wherein R_3 is C₁₋₅ alkyl, cycloalkyl or alkenyl. More particularly, it relates to a process for the preparation of tazarotene of Formula (III). The Invention also relates to a novel polymorphic form of tazarotene designated as Form A of tazarotene and process for producing it. The invention also relates to pharmaceutical compositions that include the Form A of tazarotene and use of said composition for treating stable plaque psoriasis and facial acne vulgaris.



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VC, VN, YU, ZA, ZM, ZW.

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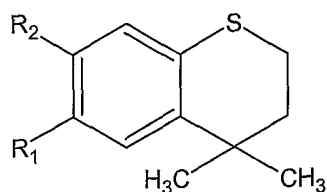
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PROCESSES FOR THE PREPARATION OF SUBSTITUTED THIOCHROMAN DERIVATIVES

Field of the Invention

The field of the invention relates to processes for the preparation of substituted
 5 thiochroman derivatives of Formula I,



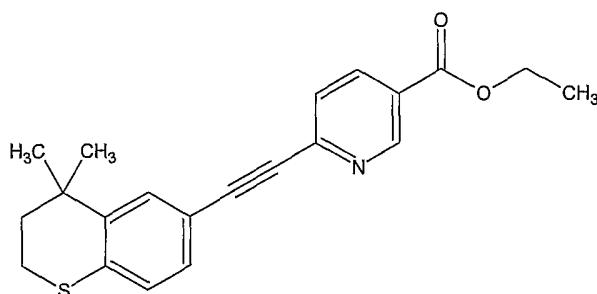
FORMULA I

wherein R₂ is hydrogen or lower alkyl; R₁ is hydrogen, halogen, a leaving group or a
 group of Formula II,



FORMULA II

wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl,
 furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a
 value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt,
 15 ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal
 derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl,
 cycloalkyl or alkenyl. More particularly, it relates to a process for the preparation of
 tazarotene of Formula III.



FORMULA III

The invention also relates to a novel polymorphic form of tazarotene designated as Form A of tazarotene and process for producing it. The invention also relates to pharmaceutical compositions that include the Form A of tazarotene and use of said compositions for treating stable plaque psoriasis and facial acne vulgaris.

5

Background of the Invention

Substituted thiochroman derivatives of Formula I are members of topically used acetylenic class of retinoids which are indicated for the topical treatment of patients with stable plaque psoriasis of up to 20% body surface area involvement and for the topical
10 treatment of patients with facial acne vulgaris of mild to moderate severity. Tazarotene is a prominent member belonging to this class of retinoids, and is commercially available in the market as Tazorac® gel and Avage® cream for topical use. Chemically, tazarotene is ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate of Formula III.

Several processes have been reported for the preparation of substituted
15 thiochroman derivatives of Formula I for example, in U.S. Patent Nos. 5,420,295; 5,519,150; International Publication No. WO 95/19973 (PCT) and European Patent No. 0 740 665.

U.S. Patent No. 5,089,509 discloses a method for the preparation of tazarotene, wherein the tazarotene is isolated as a yellow solid by flash chromatography.

20 Several processes have been reported for the preparation of intermediates required for the preparation of the compound of Formula I for example, in *Journal of Medicinal Chemistry* 1984, 27, 1516; *Journal of American Chemical Society* 1974, 94, 9158; *Chemical Letters* 1976, 523; *Journal of Organic Chemistry* 1966, 31, 413; and *Journal of Chemical Society, Chemical Communication*, 1981, 237.

25 The inventors have found that the prior art approach for the preparation of thiochroman derivatives of Formula I is not suitable from a commercial point of view because the processes are lengthy requiring isolation of several intermediates, use of toxic reagents such as isoprene bromide and yields are low.

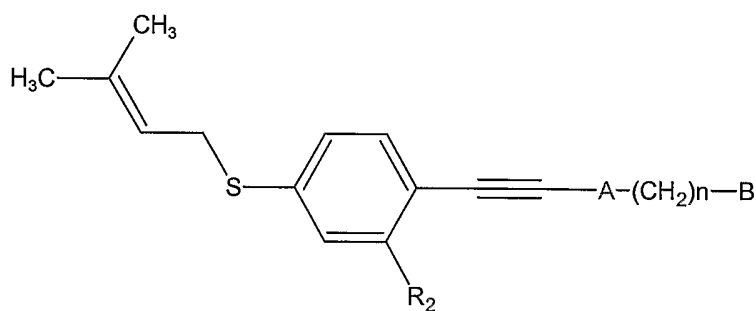
The present invention provides processes which are simple, cost-effective and easily scalable. The yield and purity of the product is greatly improved when made by the processes of the present invention.

Summary of the Invention

5 In one general aspect there are provided processes for the preparation of substituted thiochroman derivatives of Formula I.

In another general aspect there are provided processes for the preparation tazarotene of Formula III.

In another aspect there are provided compounds of Formula VI,



FORMULA VI

and a process for producing the compounds of Formula VI.

In another aspect there is provided a novel polymorphic form designated as Form A of tazarotene.

15 The Form A of tazarotene may have the X-ray diffraction pattern of Figure 1, differential scanning calorimetry plot of Figure 2, and infrared spectrum of Figure 3.

In another general aspect there is provided a process for the preparation of polymorphic Form A of tazarotene.

20 In another general aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of the Form A of tazarotene; and one or more pharmaceutically acceptable carriers, excipients or diluents.

In another aspect there is provided a method for treating stable plaque psoriasis and facial acne vulgaris in a warm-blooded animal, the method comprising providing the

warm-blooded animal a pharmaceutical composition that includes the Form A of tazarotene.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent
5 from the description and claims.

Description of the Drawings

Figure 1 is an X-ray powder diffraction pattern of Form A of tazarotene.

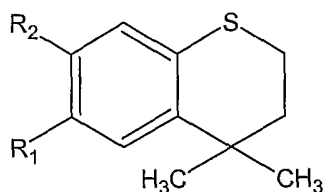
Figure 2 is a differential scanning calorimetry plot of Form A of tazarotene.

Figure 3 is an infrared spectrum of Form A of tazarotene.

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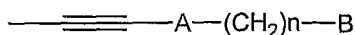
Detailed Description of the Invention

The inventors have developed a process for the preparation of substituted thiochroman derivatives of Formula I,



FORMULA I

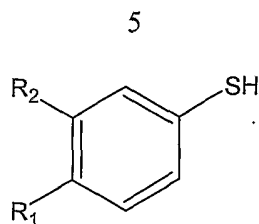
15 wherein R₂ is hydrogen or lower alkyl; R₁ is hydrogen, halogen, a leaving group or a group of Formula II,



FORMULA II

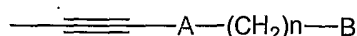
20 wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl, cycloalkyl or alkenyl, the process comprising:

25 a) treating a thiophenol derivative of Formula IV,

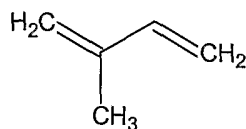
**FORMULA IV**

wherein R₂ is hydrogen or lower alkyl; R₁ is hydrogen, halogen, a leaving group or a group of Formula II,

5

**FORMULA II**

wherein A, B and n are as defined above, with a compound of Formula V,

**FORMULA V**

10 in the presence of an acid catalyst; and

b) isolating the substituted thiochroman derivative of Formula I.

The compound of Formula IV may be dissolved in an organic solvent and treated with isoprene of Formula V in the presence of an acid catalyst. The organic solvent includes one or more of aromatic hydrocarbons and halogenated aliphatic hydrocarbons.

15 The acid catalyst can be a Lewis acid or a non-Lewis acid. Examples of the acid catalysts include sulfuric acid, methane sulfonic acid, camphor sulfonic acid, trifluoromethane sulfonic acid, nitric acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid and amberlite sulfonic acid resin.

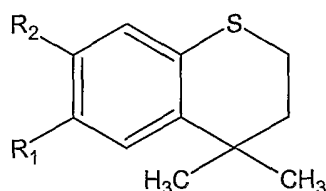
20 The reaction of the compound of Formula IV with a compound of Formula V may be exothermic and may require cooling.

The substituted thiochroman derivative may be isolated by a technique which includes for example, distillation, distillation under vacuum, cooling, extraction, filtration, filtration under vacuum, decantation and centrifugation.

After the reaction is complete, the reaction mass may be poured into a mixture of crushed ice and water. The resultant mixture may be extracted with a water immiscible organic solvent and the organic extracts may be washed subsequently with water and aqueous alkali solution. The organic extracts may be concentrated under vacuum to dryness to get a compound of Formula I.

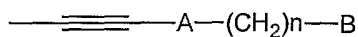
The compound of Formula I thus recovered may be further purified or additionally purified, by employing commonly practiced recrystallization techniques using solvent / antisolvent mixtures or may be purified by column chromatography.

The inventors also have developed a process for the preparation of substituted thiochroman derivatives of Formula Ia,



FORMULA Ia

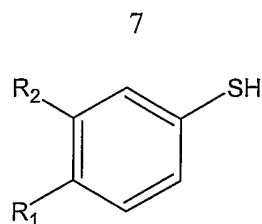
wherein R_2 is hydrogen or lower alkyl; R_1 is a group of Formula II,



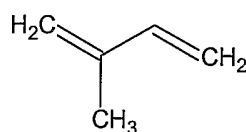
FORMULA II

wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl, cycloalkyl or alkenyl, the process comprising:

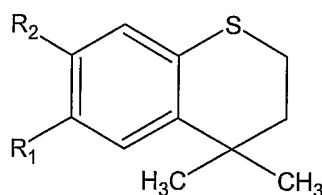
a) treating a thiophenol derivative of Formula IVa,

**FORMULA IVa**

wherein R₂ is hydrogen or lower alkyl; R₁ is halogen or a leaving group, with a compound of Formula V,

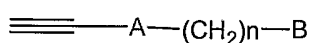
**FORMULA V**

in the presence of an acid catalyst to get a compound of Formula Ib,

**FORMULA Ib**

wherein R₁ is halogen or a leaving group and R₂ is hydrogen or lower alkyl;

b) reacting the compound of Formula Ib with a compound of Formula IIa,

**FORMULA IIa**

wherein A, B and n are as defined above; and

c) isolating the substituted thiochroman derivative of Formula Ia.

The compound of Formula IVa may be treated with isoprene of Formula V in the presence of an organic solvent containing an acid catalyst. The organic solvent includes one or more of aromatic hydrocarbons or halogenated aliphatic hydrocarbons. The acid catalyst can be a Lewis acid or a non-Lewis acid. Examples of acid catalysts include sulfuric acid, methane sulfonic acid, camphor sulfonic acid, trifluoromethane sulfonic

acid, nitric acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid and amberlite sulfonic acid resin.

5 The reaction of the compound of Formula IVa with a compound of Formula V may be exothermic and may require cooling.

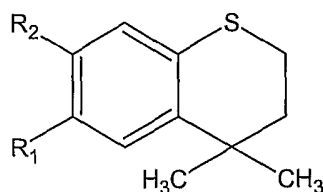
The substituted thiochroman derivative may be isolated by a technique which includes for example, distillation, distillation under vacuum, cooling, extraction, filtration, filtration under vacuum, decantation and centrifugation.

10 After the reaction is complete, the reaction mass may be poured into a mixture of crushed ice and water. The resultant mixture may be extracted with a water immiscible organic solvent and the organic extracts may be washed subsequently with water and aqueous alkali solution. The organic extracts may be concentrated under vacuum to dryness to get a compound of Formula Ib.

15 The compound of Formula Ib thus recovered may be further purified or additionally purified, by employing commonly practiced recrystallization techniques using solvent / antisolvent mixtures or may be purified by column chromatography.

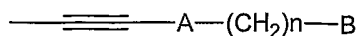
20 The compound of Formula Ib may be reacted with a compound of Formula IIa at a temperature of from about 35° to about 75°C in the presence of an alkylamine, copper salt or palladium containing catalyst for a period of about 15 to 30 hours. After completion of the reaction, the reaction may be quenched with water and extracted with a water immiscible organic solvent. The organic layer may be concentrated under vacuum to get a residue, which may be further purified by crystallization or by column chromatography to get the substituted thiochroman derivative of Formula Ia.

25 The inventors also have developed a process for the preparation of substituted thiochroman derivatives of Formula Ia,



FORMULA Ia

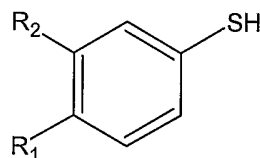
wherein R₂ is hydrogen or lower alkyl; R₁ a group of Formula II



FORMULA II

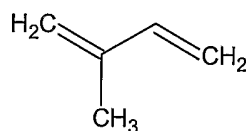
wherein, A is phenyl or heteroaryl selected from the group consisting of pyridynyl,
 5 thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer
 having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically
 acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -
 CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is
 C₁₋₅ alkyl, cycloalkyl or alkenyl, the process comprising:

10 a) treating a thiophenol derivative of Formula IVb,



FORMULA IVb

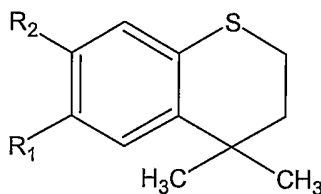
wherein R₂ is hydrogen or lower alkyl; R₁ is hydrogen, with a compound of Formula V,



15

FORMULA V

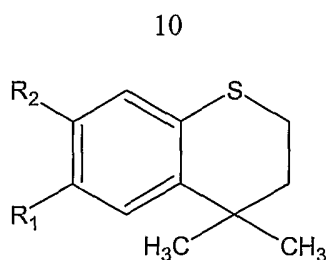
in the presence of an acid catalyst to get a compound of Formula Ic,



FORMULA Ic

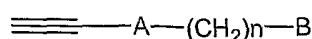
wherein R₁ is hydrogen and R₂ is hydrogen or lower alkyl;

20 b) reacting the compound of Formula Ic with a halogenating agent to get a
 compound of Formula Id,

**FORMULA Id**

wherein R_1 is halogen and R_2 is hydrogen or lower alkyl;

c) reacting the compound of Formula Id with a compound of Formula IIa,

**FORMULA IIa**

wherein A, B and n are as defined above; and

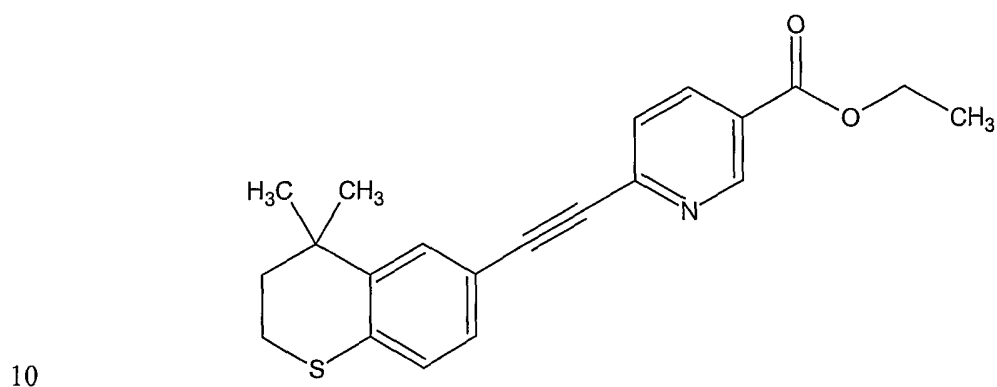
d) isolating the substituted thiochroman derivative of Formula Ia.

The compound of Formula IVb may be treated with isoprene of Formula V in the
 10 presence of an organic solvent containing an acid catalyst. The organic solvent may
 include one or more of aromatic hydrocarbons or halogenated aliphatic hydrocarbons. The
 acid catalyst can be a Lewis acid or a non-Lewis acid and may include one or more of
 sulfuric acid, methane sulfonic acid, camphor sulfonic acid, trifluoromethane sulfonic
 acid, nitric acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic
 15 acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid and amberlite sulfonic
 acid resin. The reaction may be exothermic and may require cooling. After the reaction is
 complete, the reaction mass may be poured into a mixture of crushed ice and water. The
 resultant mixture may be extracted with a water immiscible organic solvent and the
 organic extracts may be washed subsequently with water and aqueous alkali solution. The
 20 organic extracts may be concentrated under vacuum to dryness to get a compound of
 Formula Ic, which may optionally be purified by recrystallization or column
 chromatography.

The compound of Formula Ic may be reacted with a halogenating agent in the
 presence of an inert organic solvent to get a compound of Formula Id. Examples of the
 25 halogenating agent include bromine, iodine, N-halosuccinimide, and the like.

The compound of Formula Id may be reacted with a compound of Formula IIa at a temperature of from about 35° to about 75°C in the presence of an alkylamine, copper salt or palladium containing catalyst for a period of about 15 to 30 hours. After completion of the reaction, the reaction may be quenched with water and extracted with a water
 5 immiscible organic solvent. The organic layer may be concentrated under vacuum to get a residue, which may further be purified by crystallization or by column chromatography to get substituted thiochroman derivative of Formula Ia.

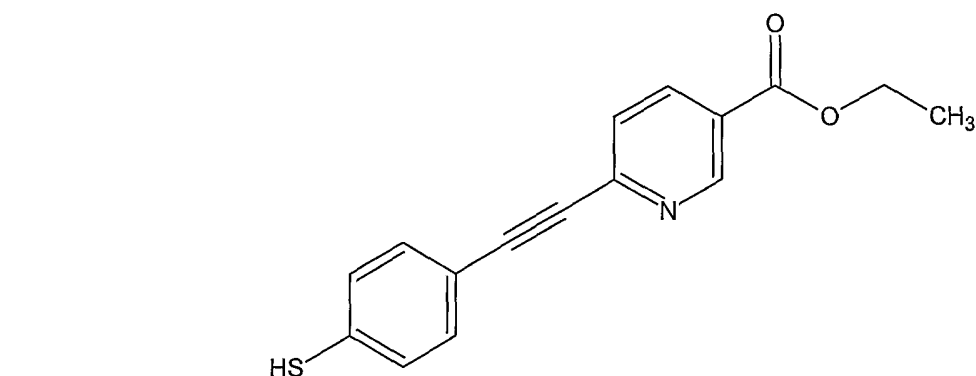
The inventors also have developed a process for the preparation of tazarotene of Formula III,



FORMULA III

the process comprising:

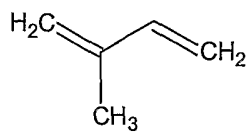
a) reacting a compound of Formula IVc,



FORMULA IVc

with a compound of Formula V,

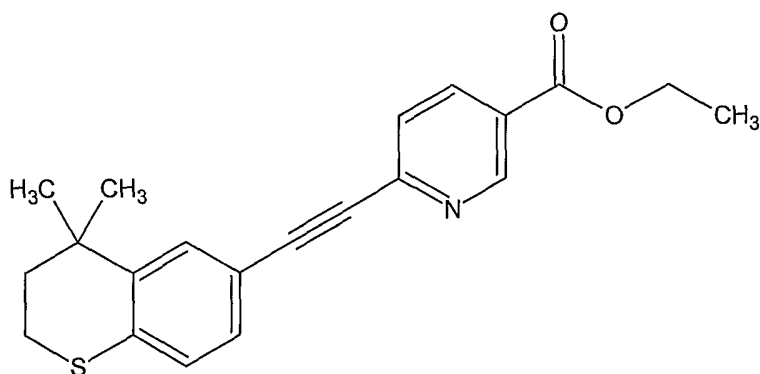
12

**FORMULA V**

in the presence of an acid catalyst; and

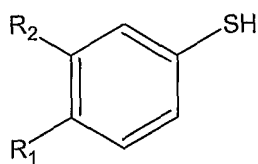
b) isolating the tazarotene of Formula III.

5 In another aspect there is provided a process for the preparation of tazarotene of Formula III,

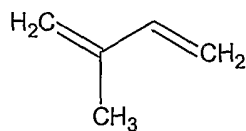
**FORMULA III**

the process comprising:

10 a) treating a thiophenol derivative of Formula IVd,

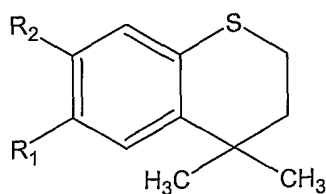
**FORMULA IVd**

wherein R_2 is hydrogen; R_1 is halogen or a leaving group, with a compound of Formula V,

**FORMULA V**

15

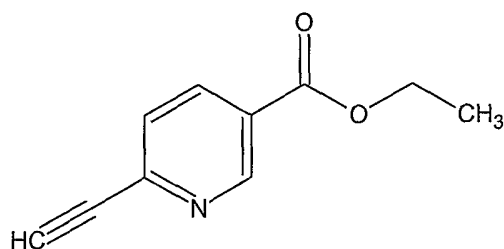
in the presence of an acid catalyst to get a compound of Formula Ie,



FORMULA Ie

wherein R₁ is halogen or a leaving group and R₂ is hydrogen;

- 5 b) reacting a compound of Formula Ie with a compound of Formula IIb; and

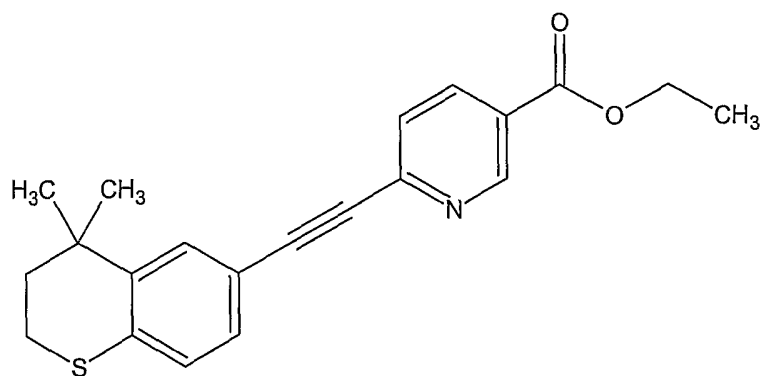


FORMULA IIb

- c) isolating the tazarotene of Formula III.

In another aspect there is provided a process for the preparation of tazarotene of

- 10 Formula III,

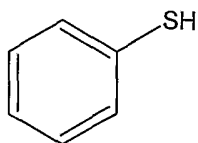


FORMULA III

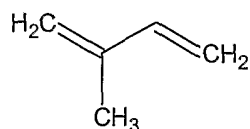
the process comprising:

- a) treating a thiophenol derivative of Formula IVe,

14

**FORMULA IVe**

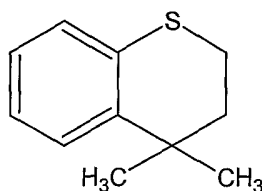
with a compound of Formula V,



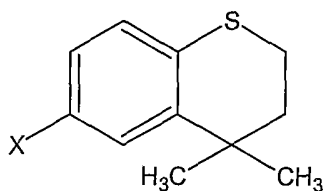
5

FORMULA V

in the presence of an acid catalyst to get a compound of Formula If;

**FORMULA If**

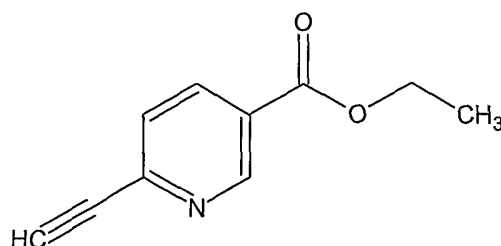
10 b) reacting the compound of Formula If with a halogenating agent to get a compound of Formula Ig,

**FORMULA Ig**

wherein X is halogen;

c) reacting the compound of Formula Ig with a compound of Formula IIb; and

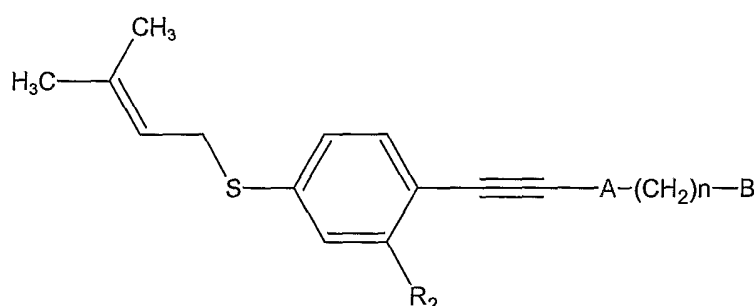
15

**FORMULA IIIb**

d) isolating the tazarotene of Formula III.

In another aspect there are provided compounds having the structure of Formula

5 VI,

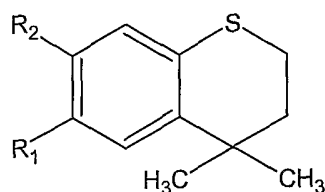
**FORMULA VI**

wherein R_2 is hydrogen or lower alkyl; A is phenyl or heteroaryl selected from the group comprising of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R_3 is C₁₋₅ alkyl, cycloalkyl or alkenyl.

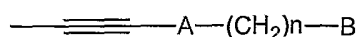
In particular, there are provided the compounds of Formula VI, wherein R_2 is hydrogen, A is selected from the group consisting of pyridyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; B is -COOH or a pharmaceutically acceptable salt or an ester thereof.

The inventors also have developed a process for the preparation of substituted thiochroman derivatives of Formula Ia,

16

**FORMULA Ia**

wherein R_2 is hydrogen or lower alkyl; R_1 is a group of Formula II,

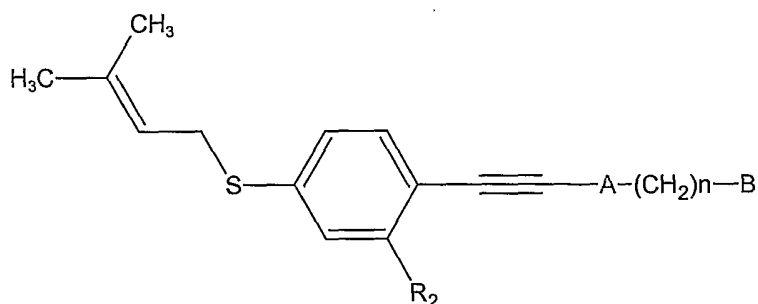


5

FORMULA II

wherein, A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R_3 is C₁₋₅ alkyl, cycloalkyl or alkenyl; the process comprising:

a) cyclizing a thiophenol derivative of Formula VI,

**FORMULA VI**

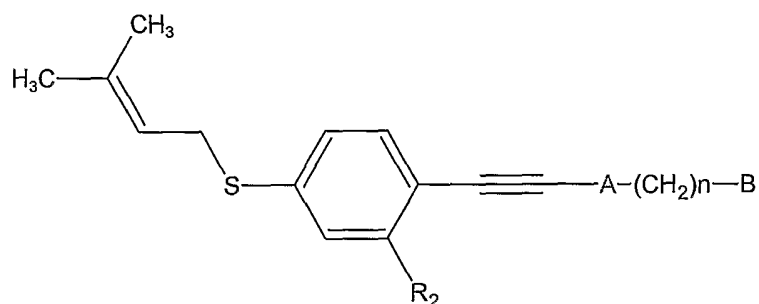
15 wherein R_2 is hydrogen or lower alkyl, and A, B and n are as defined above; and

b) isolating the compound of Formula Ia.

The compound of Formula VI may be cyclized in the presence of Lewis acids. The Lewis acid may comprise one or more of halides of aluminium, boron, tin, titanium, or iron for example, titanium chloride, aluminium chloride and boron trifluoride. The reaction may
20 also be carried out in the presence of non-Lewis acids. Examples of non-Lewis acids

include sulfuric acid, methane sulfonic acid, camphor sulfonic acid, trifluoromethane sulfonic acid, nitric acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid or amberlite sulfonic acid resin. The compound of Formula Ia may further be purified by column chromatography.

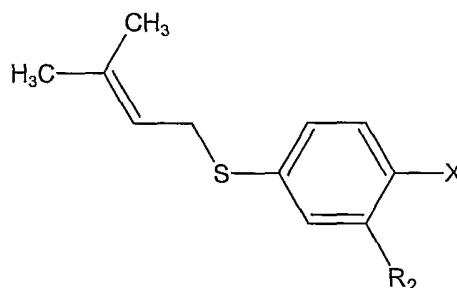
The inventors also have developed a process for the preparation of compounds of Formula VI,



FORMULA VI

wherein R_2 is hydrogen or lower alkyl; A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, $-\text{COOH}$ or its pharmaceutically acceptable salt, ester or amide thereof, $-\text{CH}_2\text{OH}$ or its ether or ester derivative thereof, $-\text{CHO}$ or an acetal derivative thereof, or $-\text{COR}_3$ or a ketal derivative thereof, wherein R_3 is C_{1-5} alkyl, cycloalkyl or alkenyl; the process comprising:

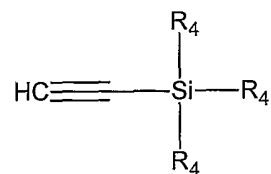
a) treating a compound of Formula VII,



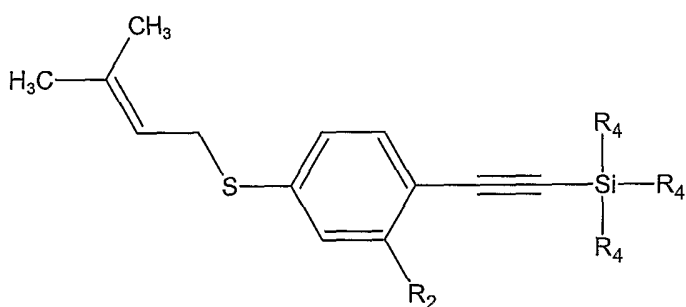
FORMULA VII

18

wherein X is halogen or a leaving group and R₂ is hydrogen or lower alkyl, with a compound of Formula VIII,

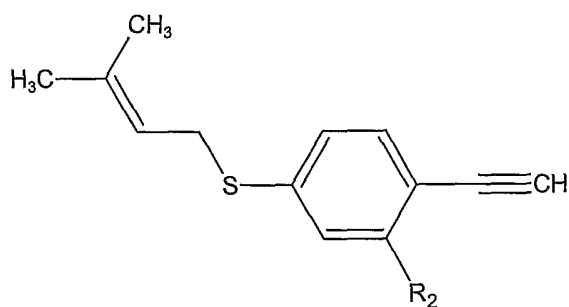
**FORMULA VIII**

5 wherein R₄ is C₁₋₅ alkyl, to get a compound of Formula IX,

**FORMULA IX**

wherein R₂ is hydrogen or lower alkyl and R₄ is C₁₋₅ alkyl;

b) desilylating the compound of Formula IX to get a compound of Formula X,

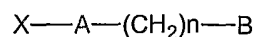


10

FORMULA X

wherein R₂ is hydrogen or lower alkyl;

c) treating the compound of Formula X with a compound of Formula IIc,



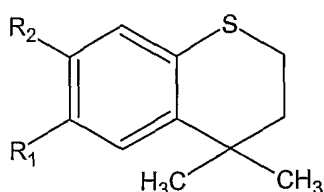
15

FORMULA IIc

wherein X is halogen or a leaving group and A, B and n are as defined above; and

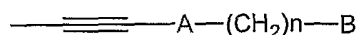
d) isolating the compound of Formula VI.

In another aspect there is provided a process for the preparation of substituted thiochroman derivatives of Formula Ia,



FORMULA Ia

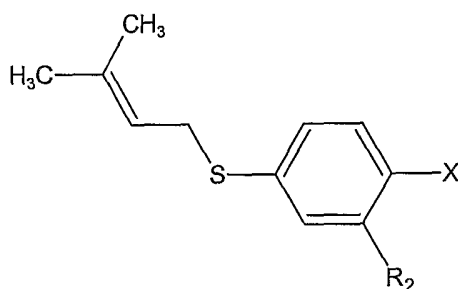
wherein R_2 is hydrogen or lower alkyl; R_1 is a group of Formula II,



FORMULA II

- 10 wherein, A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof wherein R₃ is
- 15 C₁₋₅ alkyl, cycloalkyl or alkenyl; the process comprising:

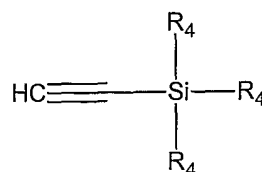
a) treating a compound of Formula VII,



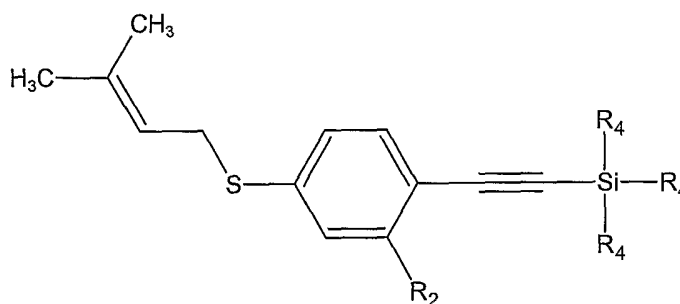
FORMULA VII

- 20 wherein X is halogen or a leaving group and R_2 is hydrogen or lower alkyl, with a compound of Formula VIII,

20

**FORMULA VIII**

wherein R_4 is C_{1-5} alkyl, to get a compound of Formula IX,

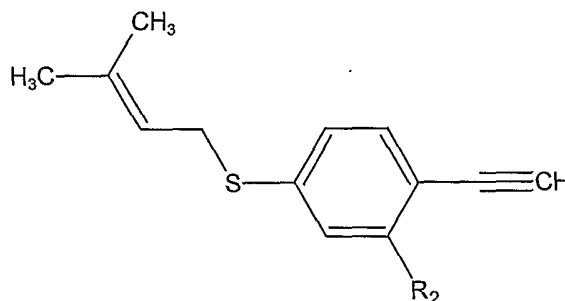


5

FORMULA IX

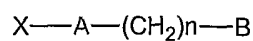
wherein R_2 is hydrogen or lower alkyl and R_4 is C_{1-5} alkyl;

b) desilylating the compound of Formula IX to get a compound of Formula X,

**FORMULA X**

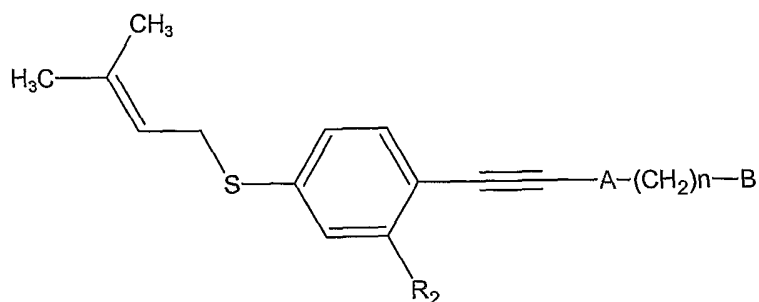
10 wherein R_2 is hydrogen or lower alkyl;

c) treating the compound of Formula X with a compound of Formula IIc,

**FORMULA IIc**

wherein X is halogen or a leaving group and A, B and n are as defined above, to get a

15 compound of Formula VI,

**FORMULA VI**

wherein R_2 is hydrogen or lower alkyl, and A, B and n are as defined above;

d) cyclizing the compound of Formula VI in the presence of an organic solvent optionally
5 containing an acid; and

e) isolating the compound of Formula Ia.

The compound of Formula VII may be treated with a trialkylsilylacetylene in the presence of a palladium catalyst and copper halide to get a compound of Formula IX. The reaction may be carried out in the presence of a base, which can also be used as a solvent.

10 The palladium catalyst may be any suitable Pd(0) or Pd(II) containing catalyst.

The compound of Formula IX may be desilylated by using an organic or inorganic base in the presence of an organic solvent. The organic solvent may be one or more of alcohols, ketones, hydrocarbons, halogenated hydrocarbons, ethers and esters. In particular, a mixture of an aqueous solution containing an inorganic base and an alkanol

15 can be used as a reaction medium.

The desilylated compound of Formula X may be treated with a compound of Formula IIc in the presence of palladium catalyst and copper halide to get a compound of Formula VI. The palladium catalyst may be any suitable Pd(0) or Pd(II) containing catalyst. The compound of Formula VI can be further purified by column chromatography.

20 The compound of Formula VI may be cyclized in the presence of an acid. The acid can be a Lewis acid and includes one or more of halides of aluminium, boron, tin, titanium or iron. The acid can also be a non-Lewis acid. Examples of non-Lewis acids include concentrated sulfuric acid, methane sulfonic acid, camphor sulfonic acid, trifluoromethane sulfonic acid, nitric acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid,

fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid and amberlite sulfonic acid resin. The cyclization may be carried out in the presence of an organic solvent for example, alcohols, ketones, hydrocarbons, halogenated hydrocarbons, aromatic hydrocarbons, nitroalkanes, ethers and esters. The reaction can be carried out in non-aqueous conditions and at a temperature of 40°C or less. A base can also be added to the reaction mixture at a temperature less than 20°C before isolating the compound of Formula Ia. The addition of base helps in neutralizing the acid present in the reaction mixture. The compound of Formula Ia may be isolated from the reaction mixture by layer separation.

10 The inventors also have found a novel polymorphic form designated as Form A of tazarotene. The Form A is characterized by its X-ray diffraction pattern as shown in Figure 1, differential scanning calorimetry plot as shown in Figure 2, and infrared spectrum as shown in figure 3.

 In general, the Form A of tazarotene may be characterized by X-ray diffraction peaks at about 10.36, 13.71, 15.16, 15.31, 16.37, 18.47, 20.81, 21.84, 23.14, 23.97, 24.34, 25.02 and 25.12 $\pm$ 0.2 degrees two-theta values. It may be further characterized by X-ray diffraction peaks at about 11.13, 12.28, 14.56, 14.74, 17.48, 18.87, 19.20, 20.25, 20.42, 21.37, 21.50, 22.32, 22.86, 26.16, 26.73, 27.00, 27.62, 28.52, 28.60, 29.37, 30.16, 30.83, 31.24, 32.01, 32.44, 32.96, 33.57, 34.10, 34.72, 35.00, 35.44, 36.35, 37.86, 38.32, 38.71 and 39.53 $\pm$ 0.2 degrees two-theta values.

 The novel polymorphic Form A may be characterized by DSC endothermic peak at 97°-110°C.

 The inventors also have developed a process for the preparation of the polymorphic Form A of tazarotene, by obtaining a solution of tazarotene in one or more organic solvents; adding a second organic solvent to the solution; and isolating the Form A of tazarotene by the removal of solvents. The inventors also have developed pharmaceutical compositions that contain the Form A of tazarotene, in admixture with one or more solid or liquid pharmaceutical diluents, carriers, and/or excipients.

In general, the solution of tazarotene may be obtained by dissolving tazarotene in one or more organic solvents. Examples of organic solvents include acetone, methyl ethyl ketone, acetonitrile, C₁₋₄ alkanol or mixtures thereof.

The solution of tazarotene in a solvent can be obtained by dissolving, slurring, stirring or a combination thereof. The solvent may be heated to obtain a solution. It may be heated at a temperature from about 40° to about 100°C for example, from about 50° to about 80°C. The solution may be filtered to remove undissolved solids. The solution may be concentrated under vacuum before adding a second organic solvent. The second organic solvent includes one or more of aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, C₂₋₇ ethers, C₃₋₁₀ cycloalkanes or mixtures thereof.

The reaction mixture may be further stirred and cooled at a temperature from about 20°C or less. Removing the solvents may include, for example, one or more of filtration, filtration under vacuum, decantation and centrifugation. The process may include further forming of the product so obtained into a finished dosage form. The resultant solid may be separated by filtration and washed with same or a different organic solvent.

The process may include further drying of the product obtained.

The solid so obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be further or additionally dried in a tray drier, dried under vacuum and/or in a Fluid Bed Drier. The resulting Form A of tazarotene is obtained as pure white crystals and is free from coloring impurities.

The tazarotene may be prepared by any of the methods known in the art including those described in U.S. Patent No. 5,089,509 and can be used as a starting material.

The resulting Form A of tazarotene may be formulated into ordinary dosage forms such as, for example, tablets, capsules, pills, solutions, etc. In these cases, the medicaments can be prepared by conventional methods with conventional pharmaceutical excipients.

The compositions include dosage forms suitable for oral, buccal, rectal, and parenteral (including subcutaneous, intramuscular, and ophthalmic) administration. The oral dosage forms may include solid dosage forms, like powder, tablets, capsules, suppositories, sachets, troches and lozenges as well as liquid suspensions, emulsions,

pastes and elixirs. Parenteral dosage forms may include intravenous infusions, sterile solutions for intramuscular, subcutaneous or intravenous administration, dry powders to be reconstituted with sterile water for parenteral administration, and the like.

5 The Form A of tazarotene can be administered for the treatment of stable plaque psoriasis and facial acne vulgaris, in a warm-blooded animal.

For the purpose of this disclosure, a warm-blooded animal is a member of the animal kingdom possessed of a homeostatic mechanism and includes mammals and birds.

10 The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Methods

15 X-ray powder diffraction patterns of the samples were recorded using X-Ray Diffractometer, Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, Divergence slits 1°, Receiving slit 0.15mm, Scatter slit 1°, Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wave length: 1.5406 Å

Infrared spectra of the samples were recorded using instrument: Perkin Elmer, 16 PC, SCAN: 16 scans, 4.0 cm⁻¹, according to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

20 Differential scanning calorimetry thermograms were recorded using DSC821 e, Mettler Toledo, Sample weight: 3-5 mg, Temperature range: 50-350° C, Heating rate: 20° C/min, Nitrogen 80.0 mL/min, Number of holes in the crucible: 1

Example 1: Preparation of 4,4-dimethylthiochroman

25 To a mixture of thiophenol (20 g) and methanesulfonic acid (28 g) in toluene (60 ml), isoprene (21 g) was added. The reaction mixture was stirred at ambient temperature for 5 hours and then cooled to 10°C followed by the addition of crushed ice (100 g). The resultant mass was extracted with ether and ether extracts were washed with water

followed by 5% aqueous sodium hydroxide solution and finally with water. The organic layer was concentrated under vacuum to get title compound as yellow oil.

Yield: 23.8 g

Example 2: Preparation of 4,4-dimethyl-6-bromothiochroman

- 5 To a mixture of 4-bromothiophenol (20 g), methanesulfonic acid (28 g) in toluene (60 ml), isoprene (20 g) was added. The reaction mass mixture stirred at ambient temperature for 5 hours and then cooled to 10°C followed by the addition of crushed ice (100 g). The resultant mass was extracted with ether and ether extracts were washed with water followed by 5% aqueous sodium hydroxide solution and finally with water. The organic
10 layer was concentrated under vacuum to get title compound as yellow oil, which was recrystallized from hexane to get white to off-white crystals of the title compound.

Yield: 27.2 g

Example 3: Preparation of 4,4-dimethyl-6-bromothiochroman

- 15 A mixture of 4,4-dimethylthiochroman (14 g) and iron filings (0.2 g) suspended in methylene chloride (120 ml) was cooled to 3°C. Bromine (13 g) was added to the reaction mass over about 3 hours while maintaining the temperature below 8°C. After the bromine addition was complete, the reaction mixture was stirred for 30 minutes and then a solution of sodium bicarbonate (9 g in 50 ml water) was added to the reaction mixture with
20 vigorous stirring. The layers were separated and the aqueous layer was extracted with methylene chloride (30 ml). The combined organic extracts were washed with water (2 x 20 ml), dried over sodium sulfate and evaporated to give crude yellow oil, which was recrystallized from hexane to get white to off-white crystals of the title compound.

Yield: 14 g.

Example 4: Preparation of ethyl 6-ethynynicotinate

A mixture of ethyl 6-iodonicotinate (10 g) in triethylamine (100 ml) was degassed under nitrogen and then successively added cuprous iodide (0.68 g), tetrakis(triphenylphosphine)palladium (2.32 g) and trimethylsilylacetylene (5.2 ml). The

mixture was stirred for 2 hours followed by the addition of water and extracted with ethyl acetate. The solvent was evaporated under vacuum and the resultant residue was dissolved in THF (50 ml). A solution of tetrabutylammonium fluoride in THF (40 ml, 1M) was added drop-wise to this mass and stirred for 2 h. The mass was finally treated with ammonium chloride solution and extracted with ethyl acetate. The organic layer was concentrated to dryness to get a residue, which was purified by chromatography to get the title compound as a solid.

Yield: 3.9 g

10 Example 5: Preparation of ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate (tazarotene)

A mixture of ethyl 6-ethynynicotinate (10 g), 4,4-dimethyl-6-bromothiochroman (14.9 g) and triethylamine (100 ml) was degassed under nitrogen followed by the addition of a mixture of cuprous iodide (14.2 g) and bis(triphenylphosphine)palladium (II) chloride (2.8 g). The reaction mixture was heated to 55°C and stirred for 20 hours at 55° to 60°C. The reaction mixture was cooled to 25°C, quenched with water and extracted with ether. The ether extracts were combined and washed with brine solution. The ethereal extracts were concentrated under vacuum and the residue was purified by chromatography to give the title compound as a white solid.

20 Yield: 20% w/w

Example 6: Preparation of tazarotene

a) Preparation of 4-bromophenyl 3-methylbut-2-en-1-yl sulfide

25 A solution of 4-bromothiophenol (15 g; 0.079 mol) and sodium hydroxide (3.17 g; 0.079 mol) in acetone (60 ml) was heated at reflux for 0.5 h followed by drop wise addition of a solution of 1-bromo-3-methyl-2-butene (11.72 g; 0.079 mol) in acetone (20 ml). The reaction mixture was heated at reflux for a further 1.5 h, cooled to 25°C and the solvent was removed in vacuum. The residue was taken up in water and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed successively with water and

sodium chloride solution. The organic layer was concentrated in vacuum to give the title compound as pale yellow oil.

Yield: 100 % w/w

5 ¹HNMR (CDCl₃, δ): 1.57 (3H, s), 1.70 (3H, s), 3.50 (2H, d, J~7.6Hz), 5.26 (1H, t, J~7.6Hz), 7.17 (2H, d, J~8.4Hz), 7.37 (2H, d, J~8.4Hz).

b) Preparation of trimethyl[4-((3-methylbut-2-en-1-yl)thio)phenyl]ethynyl]silane

A mixture of 4-bromophenyl-3-methylbut-2-en-1-yl sulfide (68 g; 0.265 mol) and
10 trimethylsilylacetylene (32 g; 0.326 mol) in triethylamine (100 ml) was degassed under argon for 15 minutes, followed by the addition of cuprous iodide (3.55 g; 0.186 mol) and tetrakis(triphenyl phosphine)palladium (14.3 g; 0.012 mol). The reaction mixture was heated at 90°C for 7 h and then cooled to 25°C. Hexane (700 ml) was added to the reaction mixture and stirred for 30 minutes followed by filtration through celite bed and washing
15 with water. The organic layer was then evaporated to get the title compound as dark brown oil.

Yield: 73 g

¹HNMR (CDCl₃, δ): 0.24 (9H, s), 3.52 (2H, t, J~7.5Hz), 5.27 (1H, t, J~7.5Hz), 7.11 – 7.39 (4H, m).

20

c) Preparation of 4-ethynylphenyl 3-methylbut-2-en-1-yl sulfide

A mixture of trimethyl[4-((3-methylbut-2-en-1-yl)thio) phenyl] ethynyl]silane (73 g; 0.265 mol) and 1 N aqueous potassium hydroxide solution (170 ml) in isopropyl alcohol (550 ml) for 5 h at 25°C. Completion of the reaction was monitored by thin layer
25 chromatography, followed by filtration through celite bed and washing with isopropyl alcohol (50 ml). The reaction mixture was concentrated under vacuum, followed by the addition of water (220 ml) to the residue and extraction with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated to get the title compound.

Yield: 40 g

¹HNMR (CDCl₃, δ): 1.62 (3H, s), 1.71 (3H, s), 3.07 (1H, s), 3.54 (2H, d, J~7.6Hz), 5.28 (1H, t, J~7.6Hz), 7.22 (2H, d, J~8.2Hz), 7.37 (2H, d, J~8.2Hz).

d) Preparation of ethyl 6-[4-((3-methylbut-2-en-1-yl)thio)phenyl]ethynyl]nicotinate

- 5 A reaction mixture of 4-ethynyl-phenyl-3-methylbut-2-en-1-ylsulfide (72 g; 0.356 mol), ethyl 6-chloronicotinate (126 g; 0.679 mol) and triethylamine (360 ml) was degassed with argon for 15 minutes, followed by the addition of tetrakis(triphenyl phosphine)palladium (20.9 g; 0.018 mol) and copper (I) iodide (7.2 g; 0.038 mol). The reaction mixture was heated at 80° to 85°C for 18 h and cooled to 25°C, followed by the addition of 50% ethyl acetate in hexane (360 ml) and stirring for 30 minutes. The reaction mixture was filtered through celite bed and washed the filtrate with water. The organic layer was evaporated to get brown colored solid material which was purified by column chromatography using 15% ethyl acetate in hexane to get the title compound.

Yield: 35.3 g

- 15 ¹HNMR (CDCl₃, δ): 1.62 (3H, s), 1.71 (3H, s), 3.07 (1H, s), 3.54 (2H, d, J~7.6Hz), 5.28 (1H, t, J~7.6Hz), 7.22 (2H, d, J~8.2Hz), 7.37 (2H, d, J~8.2Hz).

e) Preparation of ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate (tazarotene)

- 20 Ethyl 6-[4-((3-methylbut-2-en-1-yl)thio)phenyl]ethynyl]nicotinate (0.5 g) was dissolved in dichloromethane (25 ml) and cooled to 0°C. Titanium chloride (1.6 g) in dichloromethane (25 ml) was added slowly at about 5°C, then the temperature was raised to 25°C and stirred for 12 h. It was followed by the addition of water and the pH was adjusted to basic condition with triethylamine. The precipitated solids were filtered through celite bed. The layers were separated and the organic layer was evaporated to get the title compound.

Yield: 67% w/w

¹HNMR (CDCl₃, δ): 1.34 (6H, s), 1.42 (3H, t, J~6.9Hz), 1.96 (2H, t, J~6 Hz), 3.05 (2H, t, J~6 Hz), 4.45 (2H, q, J~7.3Hz), 7.08 (1H, d, J~8.2Hz), 7.26 (1H, d, J~8.2Hz), 7.57 (1H, d, J~8.1Hz), 7.62 (1H, s), 8.27 (1H, d, J~8.1Hz), 9.19 (1H, s).

Example 7: Preparation of tazarotene

A solution of ethyl 6-[4-((3-methylbut-2-en-1-yl)thio)phenyl]ethynyl]nicotinate (100 g) in dichloromethane (1 L) was added into a mixture of methane sulphonic acid (1 Kg) and dichloromethane (1 L) at 25°C. The reaction mixture was stirred for 5 minutes, followed
5 by quenching with ethyl acetate (6 L). The reaction mixture was cooled to 10°C, followed by the addition of water (1 L) and the pH was adjusted to neutral using 15% sodium hydroxide solution at 10° to 15°C. The layers were separated and the organic layer was evaporated under vacuum to get brown colored gummy solid (100 g). The solid so obtained was purified by column chromatography (15% ethyl acetate in hexanes) and
10 crystallized using ethyl acetate to get the title compound.

Yield: 33 % w/w

HPLC Purity: 99%

Example 8: Preparation of tazarotene

15 Using the procedure set forth in Example 7, dichloromethane was replaced with nitromethane (1 L) to obtain the title compound.

Yield: 68.12 % w/w

Example 9: Preparation of tazarotene

20 Using the procedure set forth in Example 7, methane sulphonic acid was replaced with concentrated sulfuric acid (1 Kg) to obtain the title compound.

Yield: 54.39 % w/w

Example 10: Preparation of tazarotene

25 Using the procedure set forth in Example 7, methane sulphonic acid was replaced with triflic acid (1 Kg) to obtain the title compound.

Yield: 48.25 % w/w

Example 11: Preparation of tazarotene

Ethyl 6-[{4-((3-methylbut-2-en-1-yl)thio)phenyl}ethynyl]nicotinate (100 g) was added into a slurry of aluminium chloride (0.4 Kg) and dichloromethane (1 L) at 25°C. The reaction mixture was stirred for 5 minutes and quenched with ethyl acetate (6 L). The
5 reaction mixture was cooled to 10°C, followed by the addition of water (1 L) and the pH was adjusted to neutral using 15% sodium hydroxide solution at 10° to 15°C. The reaction mixture so obtained was filtered through celite bed and the layers were separated. The organic layer was evaporated under vacuum and purified by column chromatography (15% ethyl acetate in hexanes) to get the title compound.
10 Yield: 45 % w/w

Example 12: Preparation of tazarotene

Using the procedure set forth in Example 11, aluminium chloride was replaced with boron trifluoride etherate (0.4 Kg) to obtain the title compound.
15 Yield: 33.80 % w/w

Example 13: Preparation of tazarotene

Using the procedure set forth in Example 11, aluminium chloride was replaced with boron trifluoride dihydrate (0.4 Kg) to obtain the title compound.
20 Yield: 74.50 % w/w

Example 14: Preparation of Form A of tazarotene

Crude tazarotene (5 g) was dissolved in acetone (15 ml) at 45° to 50°C. The solution so obtained was charged with activated charcoal (0.25 g) and stirred for 30 minutes at 45° to
25 50°C. The solution was filtered through celite bed and washed with acetone (5 ml). The filtered solution was distilled under vacuum to obtain the volume of 10 ml of acetone followed by the addition of hexanes (20 ml). The reaction mixture was cooled to 25°C and stirred for 30 minutes. The reaction mixture was further cooled to 10°C and stirred for 1

hour. The reaction mass was filtered and washed with hexanes (10 ml). The solid was dried under vacuum at ambient temperature to get 3.7 g of title compound as white crystalline powder.

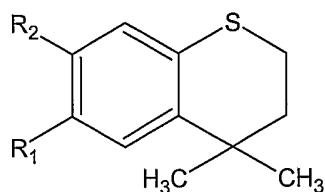
Yield: 3.7 g

5 HPLC purity: 99%

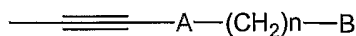
While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

1. A process for the preparation of substituted thiochroman derivatives of Formula I,

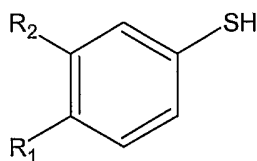
**FORMULA I**

- wherein R_2 is hydrogen or lower alkyl, R_1 is hydrogen, halogen, a leaving group or a group of Formula II,

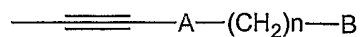
**FORMULA II**

- wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl, cycloalkyl or alkenyl, the process comprising:

- a) treating a thiophenol derivative of Formula IV,

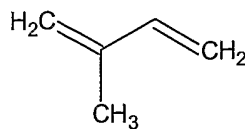
**FORMULA IV**

- wherein R_2 is hydrogen or lower alkyl; R_1 is hydrogen, halogen, a leaving group or a group of Formula II,

**FORMULA II**

- wherein A, B and n are as defined above, with a compound of Formula V,

33

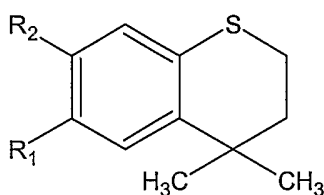
**FORMULA V**

in the presence of an acid catalyst; and

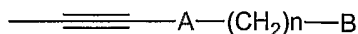
b) isolating the substituted thiochroman derivative of Formula I.

2. The process of claim 1, wherein the acid catalyst comprises one or more of sulfuric acid, methane sulfonic acid, camphor sulfonic acid, trifluoromethane sulfonic acid, nitric acid, chloroacetic acid, dichloroacetic acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid, chlorosulfonic acid and amberlite sulfonic acid resin.

3. A process for the preparation of substituted thiochroman derivatives of Formula Ia,

**FORMULA Ia**

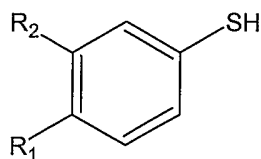
wherein R_2 is hydrogen or lower alkyl, R_1 is a group of Formula II,

**FORMULA II**

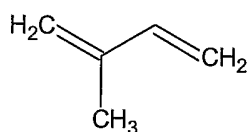
wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl, cycloalkyl or alkenyl, the process comprising:

a) treating a thiophenol derivative of Formula IVa,

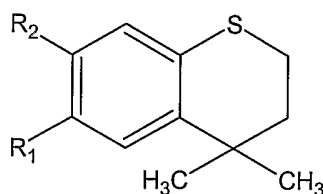
34

**FORMULA IVa**

wherein R_2 is hydrogen or lower alkyl; R_1 is halogen or a leaving group, with a compound of Formula V,

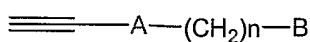
**FORMULA V**

in the presence of an acid catalyst to get a compound of Formula Ib,

**FORMULA Ib**

wherein R_1 is halogen or a leaving group and R_2 is hydrogen or lower alkyl;

b) reacting the compound of Formula Ib with a compound of Formula IIa,

**FORMULA IIa**

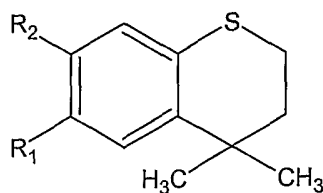
wherein A, B and n are as defined above; and

c) isolating the substituted thiochroman derivative of Formula Ia.

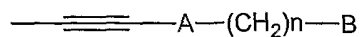
4. The process of claim 3, wherein the step b) is carried out in the presence of a palladium catalyst or a copper salt.

5. A process for the preparation of substituted thiochroman derivatives of Formula Ia,

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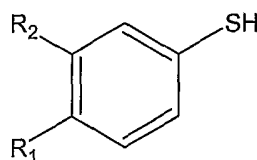
**FORMULA Ia**

wherein R_2 is hydrogen or lower alkyl; R_1 a group of Formula II,

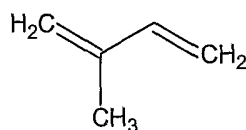
**FORMULA II**

wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R_3 is C₁₋₅ alkyl, cycloalkyl or alkenyl, the process comprising:

a) treating a thiophenol derivative of Formula IVb,

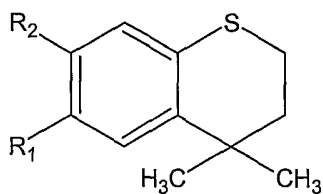
**FORMULA IVb**

wherein R_2 is hydrogen or lower alkyl; R_1 is hydrogen, with a compound of Formula V,

**FORMULA V**

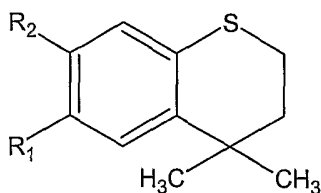
in the presence of an acid catalyst to get a compound of Formula Ic,

36

**FORMULA Ic**

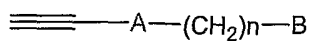
wherein R₁ is hydrogen and R₂ is hydrogen or lower alkyl;

b) reacting the compound of Formula Ic with a halogenating agent to get a compound of Formula Id,

**FORMULA Id**

wherein R₁ is halogen and R₂ is hydrogen or lower alkyl;

c) reacting the compound of Formula Id with a compound of Formula IIa,

**FORMULA IIa**

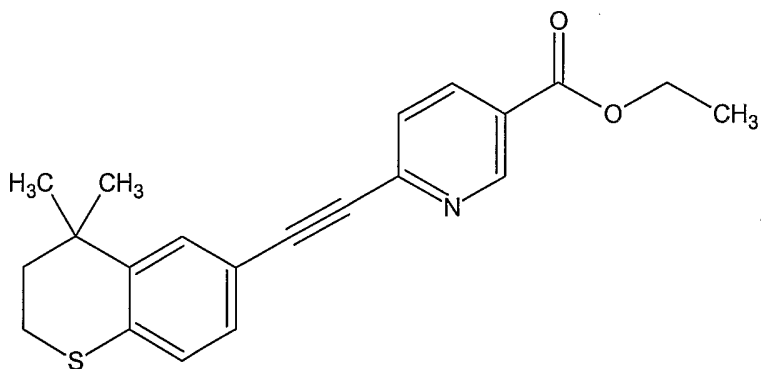
wherein A, B and n are as defined above; and

d) isolating the substituted thiochroman derivative of Formula Ia.

6. The process of claim 5, wherein the halogenating agent comprises one or more of bromine, iodine and N-halosuccinimide.

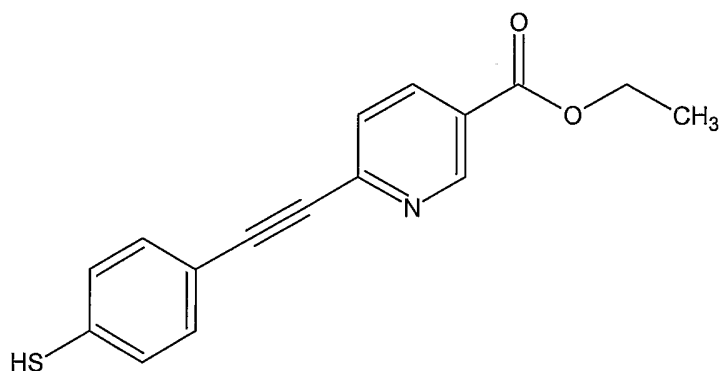
7. A process for the preparation of tazarotene of Formula III,

37

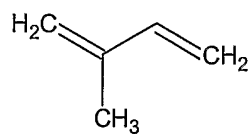
**FORMULA III**

the process comprising:

a) reacting a compound of Formula IVc,

**FORMULA IVc**

with a compound of Formula V,

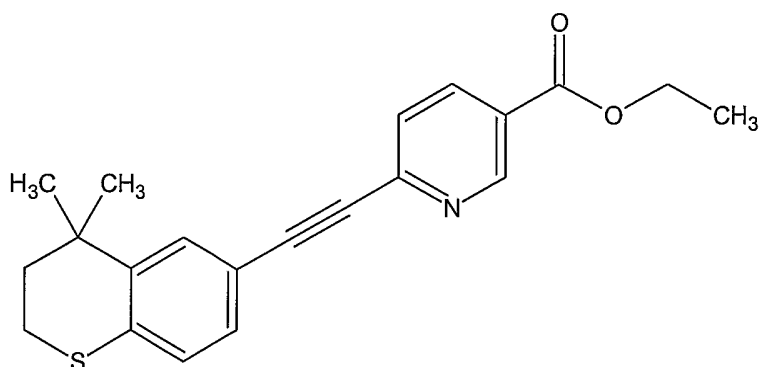
**FORMULA V**

in the presence of an acid catalyst; and

b) isolating the tazarotene of Formula III.

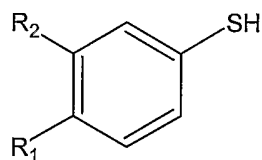
8. A process for the preparation of tazarotene of Formula III,

38

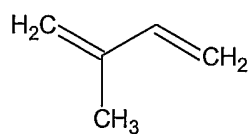
**FORMULA III**

the process comprising:

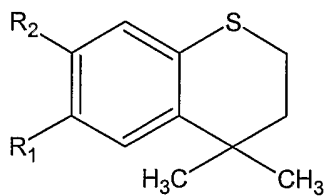
a) treating a thiophenol derivative of Formula IVd,

**FORMULA IVd**

wherein R₂ is hydrogen; R₁ is halogen or a leaving group, with a compound of Formula V,

**FORMULA V**

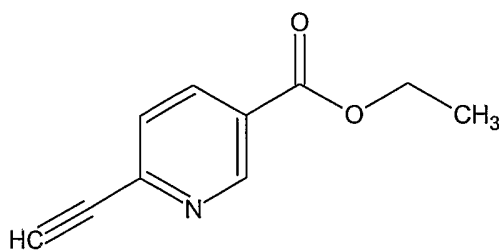
in the presence of an acid catalyst to get a compound of Formula Ie,

**FORMULA Ie**

wherein R₁ is halogen or a leaving group and R₂ is hydrogen;

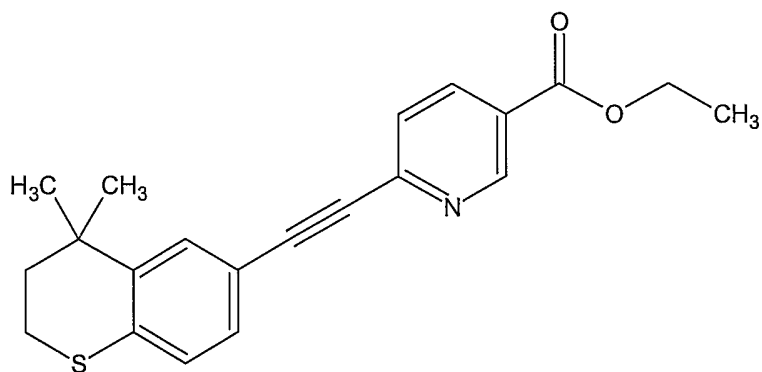
b) reacting the compound of Formula Ie with a compound of Formula IIb; and

39

**FORMULA IIb**

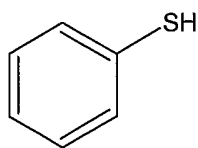
c) isolating the tazarotene of Formula III.

9. A process for the preparation of tazarotene of Formula III,

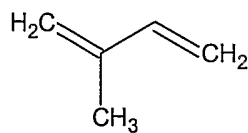
**FORMULA III**

the process comprising:

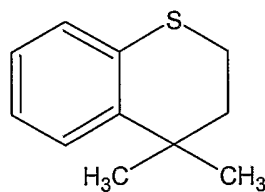
a) treating a thiophenol derivative of Formula IVe,

**FORMULA IVe**

with a compound of Formula V,

**FORMULA V**

11 in the presence of an acid catalyst to get a compound of Formula If;



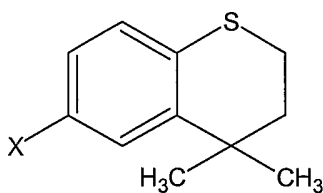
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13

FORMULA If

14 b) reacting the compound of Formula If with a halogenating agent to get a

15 compound of Formula Ig,



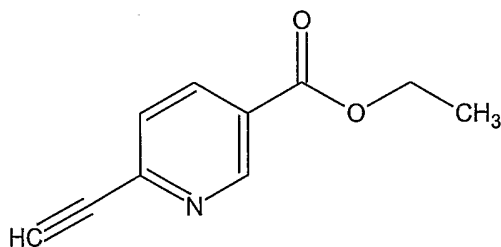
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17

FORMULA Ig

18 wherein X is halogen;

19 c) reacting the compound of Formula Ig with a compound of Formula IIb; and



20

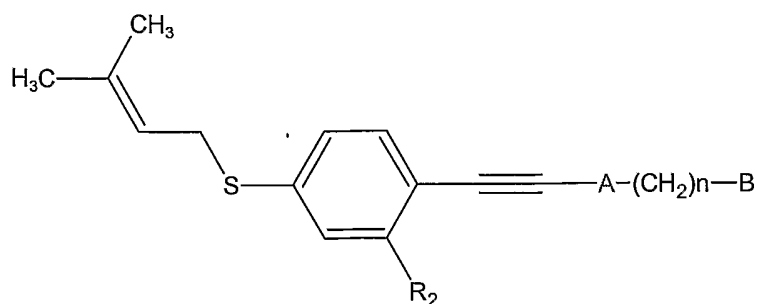
21

FORMULA IIb

22 d) isolating the tazarotene of Formula III.

1 10. Compounds having the structure of Formula VI,

41



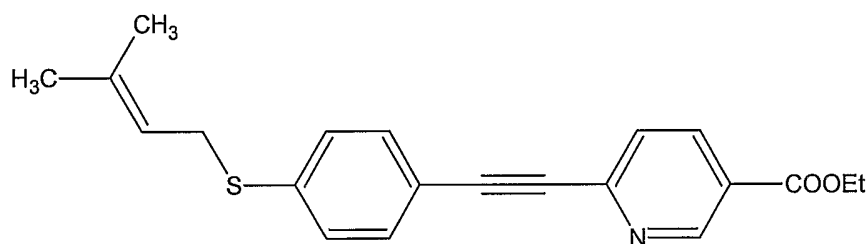
2

3

FORMULA VI

4 wherein R_2 is hydrogen or lower alkyl; A is phenyl or heteroaryl selected from the group
 5 consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or
 6 oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, -COOH or its
 7 pharmaceutically acceptable salt, ester or amide thereof, -CH₂OH or its ether or ester
 8 derivative thereof, -CHO or an acetal derivative thereof, or -COR₃ or a ketal derivative
 9 thereof, wherein R_3 is C₁₋₅ alkyl, cycloalkyl or alkenyl.

1 11. The compound of claim 10, having the structure of Formula VIa.

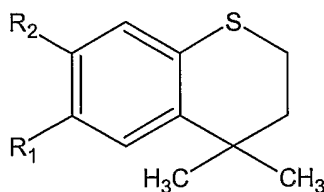


2

3

FORMULA VIa

1 12. A process for the preparation of substituted thiochroman derivatives of Formula Ia,



2

3

FORMULA Ia

4 wherein R_2 is hydrogen or lower alkyl; R_1 is a group of Formula II,

5

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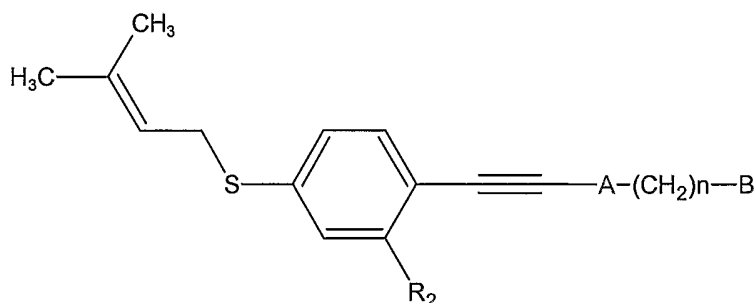


7

FORMULA II

8 wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl,
 9 furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a
 10 value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt,
 11 ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal
 12 derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl,
 13 cycloalkyl or alkenyl; the process comprising:

14 a) cyclizing a thiophenol derivative of Formula VI,



15

16

FORMULA VI

17 wherein R₂ is hydrogen or lower alkyl, and A, B and n are as defined above; and

18 b) isolating the compound of Formula Ia.

1 13. The process of claim 12, wherein the step a) is carried out in the presence of a
 2 Lewis acid comprising one or more of halides of aluminium, boron, tin, titanium, or iron.

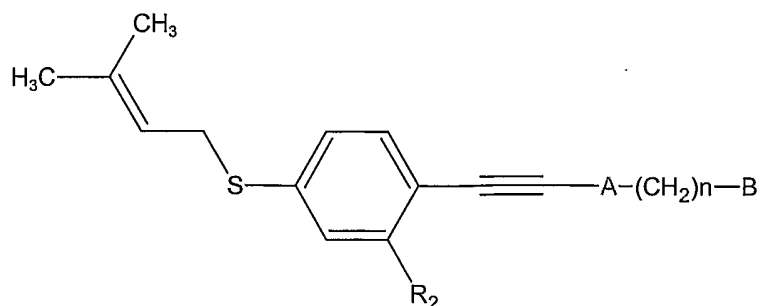
1 14. The process of claim 13, wherein the Lewis acid is titanium chloride, aluminium
 2 chloride or boron trifluoride.

1 15. The process of claim 12, wherein the step a) is carried out in the presence of a non-
 2 Lewis acid comprising one or more of sulfuric acid, methane sulfonic acid, camphor
 3 sulfonic acid, trifluoromethane sulfonic acid, nitric acid, chloroacetic acid, dichloroacetic
 4 acid, trichloroacetic acid, fluoroacetic acid, difluoroacetic acid, trifluoroacetic acid,
 5 chlorosulfonic acid or amberlite sulfonic acid resin.

1 16. The process of claims 12, wherein the compound of Formula Ia is tazarotene.

1 17. The process of claims 12, further comprising purification of the compound of
 2 Formula Ia by column chromatography.

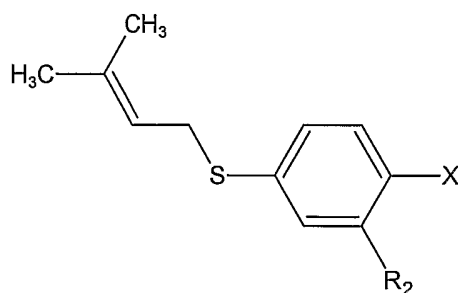
1 18. A process for the preparation of compounds of Formula VI,



3 **FORMULA VI**

4 wherein R_2 is hydrogen or lower alkyl; A is phenyl or heteroaryl selected from the group
 5 consisting of pyridynyl, thienyl, furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or
 6 oxazolyl; n is an integer having a value between 0 to 5; and B is hydrogen, $-COOH$ or its
 7 pharmaceutically acceptable salt, ester or amide thereof, $-CH_2OH$ or its ether or ester
 8 derivative thereof, $-CHO$ or an acetal derivative thereof, or $-COR_3$ or a ketal derivative
 9 thereof, wherein R_3 is C_{1-5} alkyl, cycloalkyl or alkenyl; the process comprising:

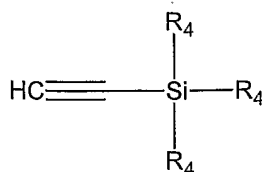
10 a) treating a compound of Formula VII,



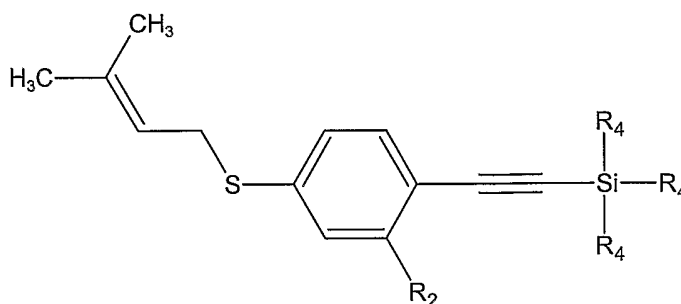
12 **FORMULA VII**

13 wherein X is halogen or a leaving group and R_2 is hydrogen or lower alkyl, with a
 14 compound of Formula VIII,

44

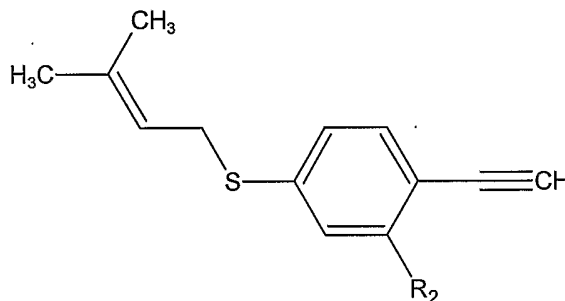
**FORMULA VIII**

wherein R₄ is C₁₋₅ alkyl, to get a compound of Formula IX,

**FORMULA IX**

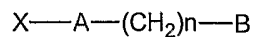
wherein R₂ is hydrogen or lower alkyl and R₄ is C₁₋₅ alkyl;

b) desilylating the compound of Formula IX to get a compound of Formula X,

**FORMULA X**

wherein R₂ is hydrogen or lower alkyl;

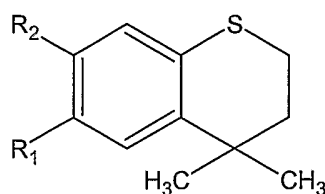
c) treating the compound of Formula X with a compound of Formula IIc,

**FORMULA IIc**

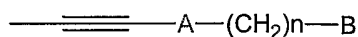
wherein X is halogen or a leaving group and A, B and n are as defined above; and

d) isolating the compound of Formula VI.

- 1 19. The process of claim 18, wherein the compound of Formula VIII is
2 trimethylsilylacetylene.
- 1 20. The process of claim 18, wherein the desilylation is carried out in the presence of
2 an organic or inorganic base.
- 1 21. The process of claim 18, wherein the step a) is carried out in the presence of a
2 palladium catalyst.
- 1 22. The process of claim 18, wherein the step c) is carried out in the presence of a
2 palladium catalyst.
- 1 23. A process for the preparation of substituted thiochroman derivatives of Formula Ia,

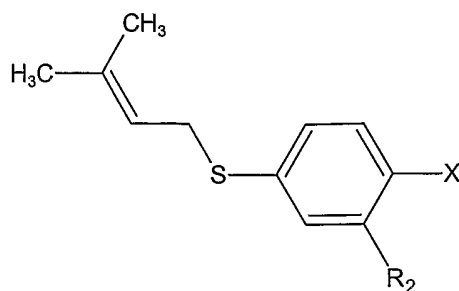
**FORMULA Ia**

4 wherein R_2 is hydrogen or lower alkyl; R_1 is a group of Formula II,

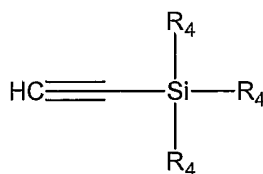
**FORMULA II**

- 7 wherein A is phenyl or heteroaryl selected from the group consisting of pyridynyl, thienyl,
8 furyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiazolyl or oxazolyl; n is an integer having a
9 value between 0 to 5; and B is hydrogen, -COOH or its pharmaceutically acceptable salt,
10 ester or amide thereof, -CH₂OH or its ether or ester derivative thereof, -CHO or an acetal
11 derivative thereof, or -COR₃ or a ketal derivative thereof, wherein R₃ is C₁₋₅ alkyl,
12 cycloalkyl or alkenyl; the process comprising:
- 13 a) treating a compound of Formula VII,

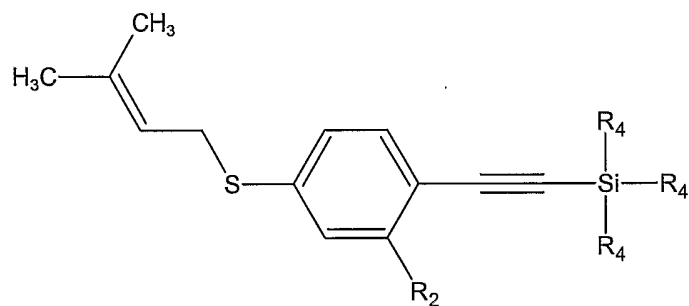
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**FORMULA VII**

wherein X is halogen or a leaving group and R₂ is hydrogen or lower alkyl, with a compound of Formula VIII,

**FORMULA VIII**

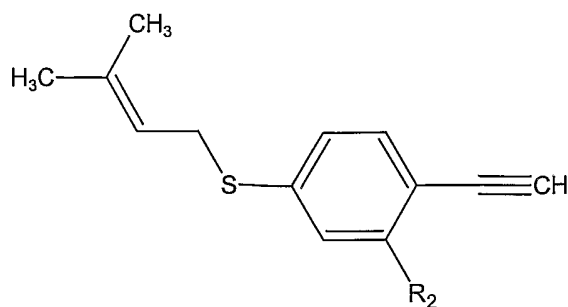
wherein R₄ is C₁₋₅ alkyl, to get a compound of Formula IX,

**FORMULA IX**

wherein R₂ is hydrogen or lower alkyl and R₄ is C₁₋₅ alkyl;

b) desilylating the compound of Formula IX to get a compound of Formula X,

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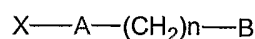
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FORMULA X27 wherein R_2 is hydrogen or lower alkyl;

28 c) treating the compound of Formula X with a compound of Formula IIc,

29

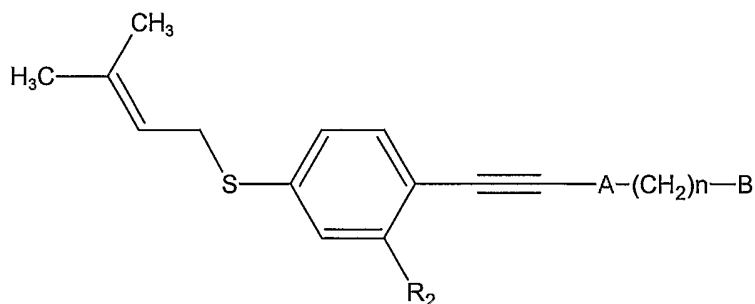


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FORMULA IIc

31 wherein X is halogen or a leaving group and A, B and n are as defined above, to get a

32 compound of Formula VI,



33

34

FORMULA VI35 wherein R_2 is hydrogen or lower alkyl, and A, B and n are as defined above;

36 d) cyclizing the compound of Formula VI in the presence of an organic solvent

37 optionally containing an acid; and

38 e) isolating the compound of Formula Ia.

1 24. The process of claim 23, wherein the step a) is carried out in the presence of an
2 acid.

1 25. The process of claim 24, wherein the acid is a Lewis acid.

- 1 26. Polymorphic Form A of tazarotene.
- 1 27. The polymorphic Form A of claim 26, wherein the tazarotene has the X-ray
2 diffraction pattern of Figure 1.
- 1 28. The polymorphic Form A of claim 26 having characteristic X-ray diffraction peaks
2 at about 10.36, 13.71, 15.16, 15.31, 16.37, 18.47, 20.81, 21.84, 23.14, 23.97, 24.34, 25.02
3 and 25.12 ± 0.2 degrees two-theta values.
- 1 29. The polymorphic Form A of claim 28 further characterized by X-ray diffraction
2 peaks at about 11.13, 12.28, 14.56, 14.74, 17.48, 18.87, 19.20, 20.25, 20.42, 21.37, 21.50,
3 22.32, 22.86, 26.16, 26.73, 27.00, 27.62, 28.52, 28.60, 29.37, 30.16, 30.83, 31.24, 32.01,
4 32.44, 32.96, 33.57, 34.10, 34.72, 35.00, 35.44, 36.35, 37.86, 38.32, 38.71 and 39.53 ± 0.2
5 degrees two-theta values.
- 1 30. The polymorphic Form A of claim 26, wherein the tazarotene has the differential
2 scanning calorimetry plot of Figure 2 having a DSC thermogram,
- 3 31. The polymorphic Form A of claim 30 having characteristic endothermic peak at
4 97° - 110° C.
- 5 32. The polymorphic Form A of claim 26, wherein the tazarotene has the infrared
6 spectrum of Figure 3.
- 7 33. A process for the preparation of polymorphic Form A of tazarotene, the process
8 comprising:
- 9 a) obtaining a solution of tazarotene in one or more organic solvents;
- 10 b) adding a second organic solvent to the solution; and
- 11 c) isolating the Form A of tazarotene by the removal of the solvents.
- 1 34. The process of claim 33, wherein the organic solvent comprises one or more of
2 acetone, methyl ethyl ketone, acetonitrile, C_{1-4} alkanol or mixtures thereof.
- 1 35. The process of claim 33, wherein the second organic solvent comprises one or
2 more of aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, C_{2-7}
3 ethers, C_{3-10} cycloalkanes or mixtures thereof.

1 36. The process of claim 33, wherein removing the solvents comprises one or more of
2 filtration, filtration under vacuum, decantation and centrifugation.

3 37. A pharmaceutical composition comprising a therapeutically effective amount of
4 polymorphic Form A of tazarotene; and one or more pharmaceutically acceptable carriers,
5 excipients or diluents.

6 38. A method of treating stable plaque psoriasis and facial acne vulgaris in a warm-
7 blooded animal, the method comprising providing a dosage form to the warm-blooded
8 animal that includes Form A of tazarotene.

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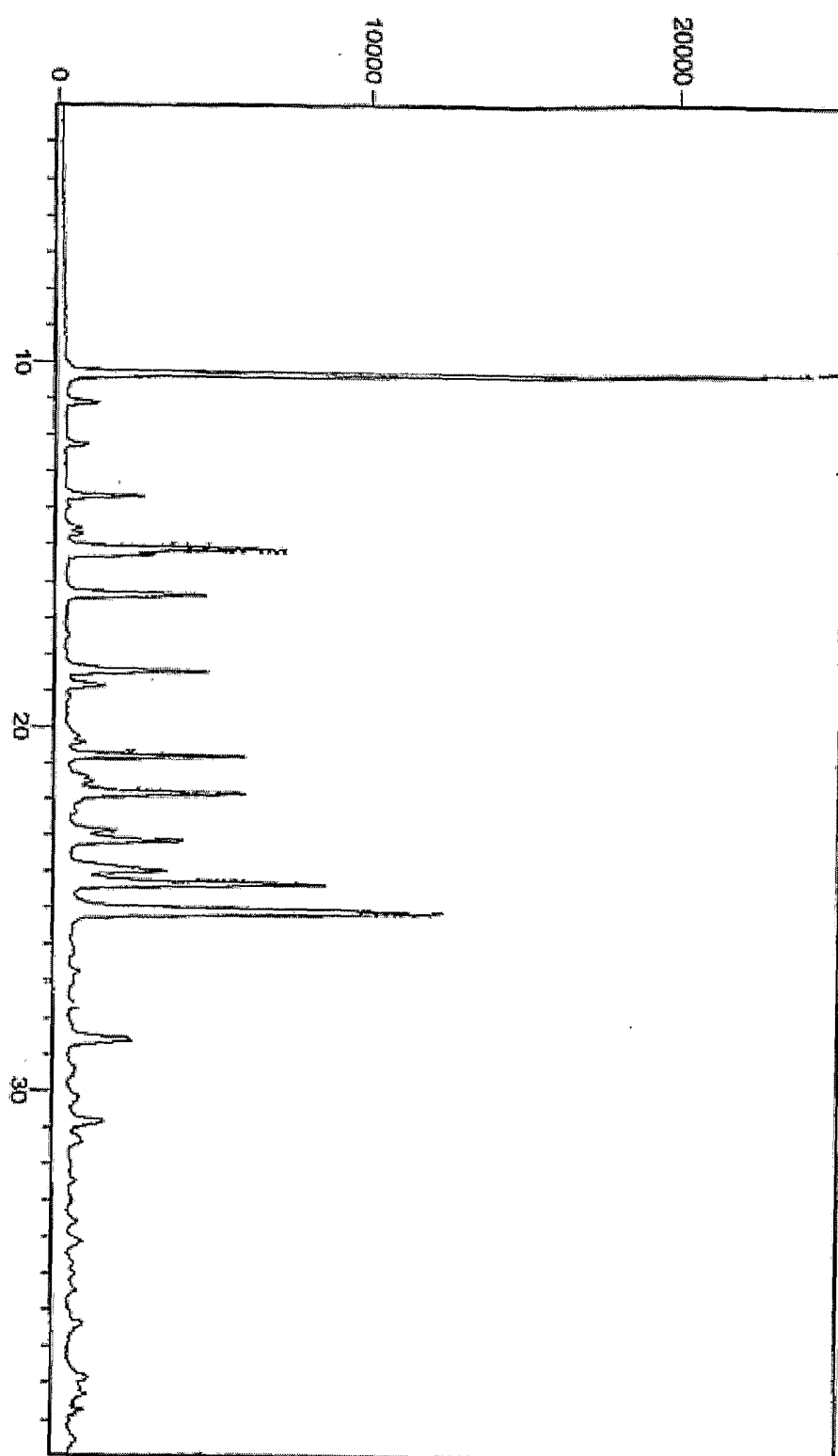
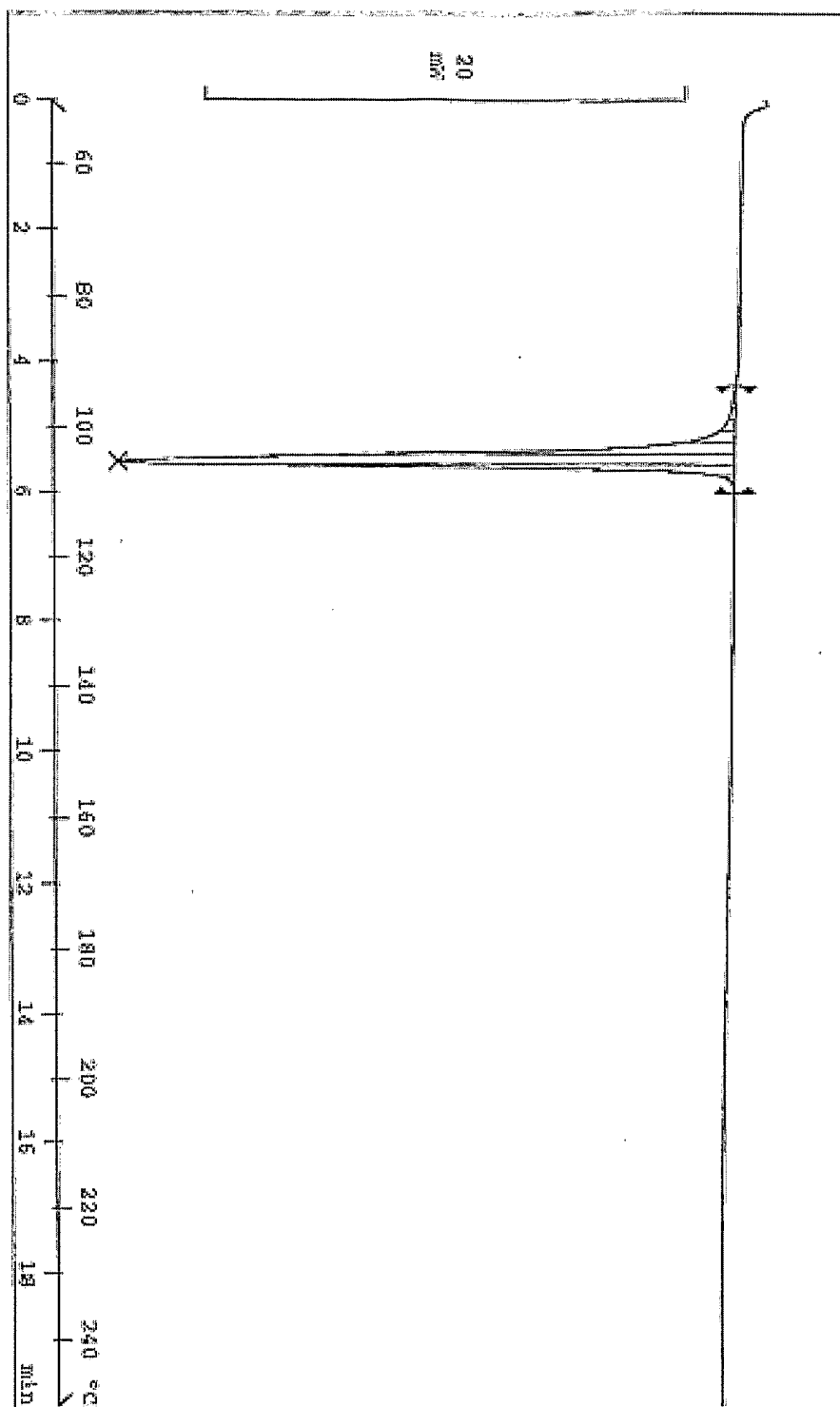


FIGURE 1: XRPD OF FORM A OF TAZAROTENE

FIGURE 2: DSC OF FORM A OF TAZAROTENE



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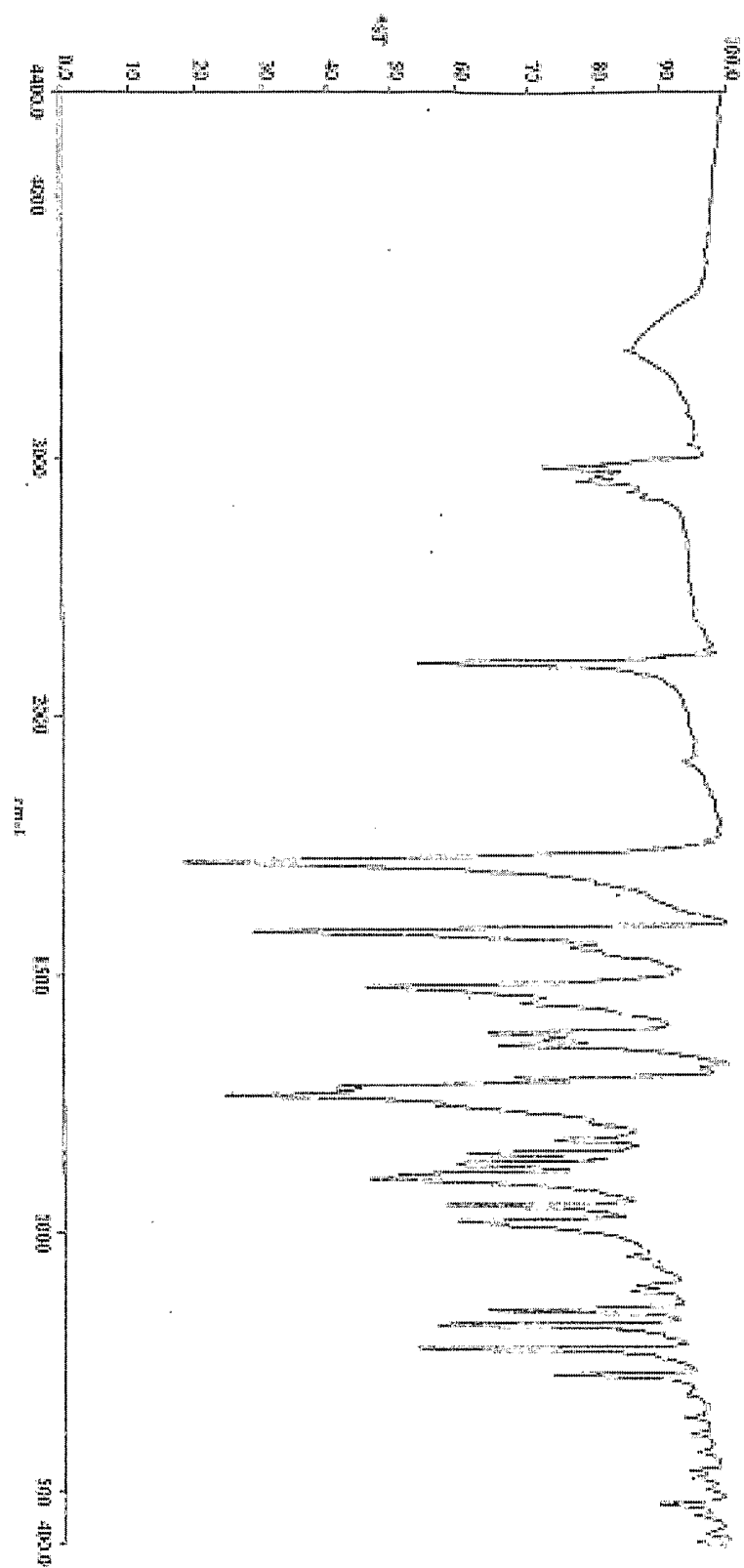


FIGURE 3: FTIR OF FORM A OF TAZARTENE